

# Comparison of sevoflurane and desflurane on effect-site concentration of remifentanyl for preventing anesthetic emergence cough in elderly female patients undergoing laparoscopic cholecystectomy

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**Purpose:** Among inhalational anesthetics, desflurane is widely believed to provoke upper airway irritation including coughing and laryngospasm. Remifentanyl has been generally used to prevent cough due to its unique pharmacodynamics. However, there was no study that compared optimal remifentanyl effect-site concentration ( $C_e$ ) to prevent emergence cough according to the type of inhalational agent in elderly female patients. Thus, we investigated the  $C_e$  of remifentanyl for preventing cough during emergence from sevoflurane and desflurane anesthesia in elderly female patients.

**Methods:** Forty-three female patients between 60 and 75 years of age undergoing laparoscopic cholecystectomy were randomly allocated to sevoflurane group ( $n=22$ ) or desflurane group ( $n=21$ ). The optimal remifentanyl  $C_e$  using target-controlled infusion for 50% of patients ( $EC_{50}$ ) and 95% of patients ( $EC_{95}$ ) was assessed by Dixon's up-and-down method or isotonic regression method with a bootstrapping approach.

**Results:** By Dixon's up-and-down method, the  $EC_{50}$  of remifentanyl in sevoflurane group ( $2.08 \pm 0.47$  ng/mL) was comparable with that in desflurane group ( $2.25 \pm 0.40$  ng/mL) ( $P=0.385$ ). The  $EC_{50}$  (83% CIs) and  $EC_{95}$  (95% CIs) by isotonic regression also did not show significant difference between two groups [ $2.06$  ( $1.45-2.23$ ) and  $2.46$  ( $2.35-2.48$ ) ng/mL in sevoflurane group and  $2.14$  ( $1.45-2.56$ ) and  $2.88$  ( $2.47-2.98$ ) ng/mL in desflurane group, respectively].

**Conclusion:** There was no difference in the remifentanyl  $C_e$  to prevent emergence cough between sevoflurane and desflurane anesthesia. Therefore, the clinicians may not need to adjust the remifentanyl  $C_e$  to prevent emergence cough according to inhalational agents in elderly female patients.

**Keywords:** aging, cough, inhalational anesthetics, opioid, women

## Introduction

Cough is a normal reaction for removing foreign body and secretion from airway. During emergence from general anesthesia, cough is caused by stimulation of the endotracheal tube, inhalational agents, or secretion.<sup>1</sup> However, cough during emergence may lead to various adverse effects including increased intraocular and intracranial pressures, wound disruption, surgical site bleeding, and detrimental hemodynamic changes.<sup>2</sup>

To prevent emergence cough, several methods have been studied, such as intravenous opioid, dexmedetomidine, ketamine, or propofol infusion or lidocaine

administration via intravenous or intraendotracheal tube cuff.<sup>3–6</sup> Of these, remifentanyl has been shown to prevent emergence cough due to its unique pharmacodynamics. It can control various levels of external stimuli even in patients with renal or hepatic dysfunction.<sup>7,8</sup> However, remifentanyl infusion may lead to respiratory depression, delayed emergence, nausea, and vomiting like other opioids.<sup>9</sup> Therefore, it is important to find the optimal effect-site concentration (Ce) of remifentanyl to have the cough inhibitory effect with minimal complications.

Various studies have been performed to evaluate the optimal Ce of remifentanyl using target-controlled infusion (TCI) for preventing emergence cough.<sup>10–14</sup> Cough reflex and a degree of airway irritation differed according to age<sup>15,16</sup> and the type of anesthetic agent.<sup>17,18</sup> Recently, the remifentanyl Ce for preventing emergence cough showed difference according to sex.<sup>19–21</sup> A study reported no difference of remifentanyl Ce between sevoflurane and desflurane for preventing emergence cough in female patients aged 20–65 years.<sup>22</sup> However, there has been no study that compared the optimal remifentanyl Ce for preventing emergence cough according to the type of inhalational agent in elderly female patients. We hypothesized that the remifentanyl Ce for preventing emergence cough in elderly female patients differs according to the type of inhalational agent because aging affects cough reflex.

The aim of the present study was to compare remifentanyl Ce for preventing cough during emergence from sevoflurane and desflurane anesthesia in elderly female patients.

## Methods

### Study population

This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB-MED-OBS-16-147) and registered at <http://cris.nih.go.kr> (KCT0002883). Written informed consent was obtained from all participants. Female patients with American Society of Anesthesiologists physical status of 1 or 2 at the age of 60–75 years who underwent scheduled laparoscopic cholecystectomy under general anesthesia were included from June 2016 to April 2018. Exclusion criteria were as follows: 1) those who had a body mass index (BMI) >30 kg/m<sup>2</sup>, uncontrolled hypertension or diabetes mellitus, or significant coronary disease; 2) those who had a history of recent upper airway infection within 2 weeks, chronic respiratory disease, difficult intubation, smoking, or chronic opioids dependency; 3) those who were illiterate, who were foreigners, who refused to participate in this study, or who lacked decision-making ability.

## Anesthetic management

After arrival in the operating room without premedication, basic monitoring including pulse oximetry, electrocardiography, and noninvasive blood pressure cuff and bispectral index (BIS™ Quatro Sensor; Covidien, Boulder, CO, USA) was performed on the patient. After preoxygenation via facial mask, anesthesia was induced with thiopental sodium 4–5 mg/kg and 1–5 ng/mL target concentration of remifentanyl (Ultiva, GlaxoSmithKline, Brentford, UK) using TCI mode based on Minto's pharmacokinetic model.<sup>23</sup> After loss of consciousness, manual mask ventilation with 100% oxygen and inhalational agent according to the assigned group [sevoflurane (Sevorane®, Abbott Laboratories, Abbott Park, IL, USA) or desflurane (Suprane®, Baxter Healthcare, Deerfield, IL, USA)] was started and followed by rocuronium (1.0 mg/kg). After enough oxygenation and muscular relaxation, orotracheal intubation was done with a cuffed endotracheal tube of 7.0 mm inner diameter. Cuff pressure was adjusted at 20–25 mmHg using a hand pressure gauge.

Mechanical ventilation was initiated with a tidal volume of 8–10 mL/kg and an inspired oxygen fraction of 0.5 at a 3 L fresh gas flow. Anesthesia was maintained using 0.7–1.3 minimal alveolar concentration (MAC) of inhalational agent and 1–3 ng/mL remifentanyl of TCI mode. Anesthetic depth was controlled using a bispectral index (BIS) value targeting 40–55 and a heart rate (HR) and mean arterial pressure (MAP) maintained within 20% of baseline. Approximately 15 minutes prior to the end of surgery, inhalational agent was reduced to a BIS value of 60, and the remifentanyl Ce was set at the predetermined Ce. Then, 30 mg of IV ketorolac and 0.3 mg of ramosetron were administered for postoperative pain control and antiemetics. At the end of surgery, inhalational agent was stopped, and the fresh gas flow was increased to 10 L/min. Sugammadex of 3 mg/kg was administered to reverse a residual neuromuscular block. Mechanical ventilation was then switched to manual ventilation while supporting the patient's spontaneous breathing. After the patients opened the eyes to verbal command without other stimulation and adequate self-ventilation was confirmed, extubation was done. Immediately after extubation, remifentanyl infusion was stopped and 100% oxygen was supplied via facial mask. After closed observation for 3 minutes, patients were transferred to the postanesthesia care unit (PACU).

## Study protocol and outcome measurement

According to randomization using R 3.4.0 (Vienna, Austria; <http://www.R-project.org/>), participants were randomly

assigned to one of the following two groups: sevoflurane group or desflurane group. By Dixon's up-and-down method, the patients were sequentially enrolled until they reached six success-failure pairs. If one group reached six success-failure pairs, then all subsequent patients were enrolled in the other group. Except in-room outcome assessor, preoperative and postoperative outcome assessors and patients were blinded to the type of intervention.

Preoperative data including age, weight, smoking history, and past medical history were collected. During anesthetic induction, intubation attempts and numbers of endotracheal tube repositioning were recorded. The data including HR, MAP, and peripheral saturation via pulse oximetry were recorded at five time points: baseline (before induction), the end of surgery, immediate before and after extubation, and 3 minutes after extubation.

Cough was defined as a sudden contraction of abdominal muscle. Cough during emergence was recorded from the end of surgery until 3 minutes after extubation. To determine the optimal remifentanyl Ce, Dixon's sequential allocation design was used. The first patient in each group was started with 2 ng/mL of remifentanyl Ce. The predetermined Ce of the next patient was set by the cough response during emergence of the previous patient. If the patient did not cough during emergence, we defined it as smooth emergence. Then, the predetermined Ce of the next patient was set 0.5 ng/mL lower than the previous patient. If the patient coughed more than once during emergence, we defined it as failed smooth emergence, and the predetermined Ce of the next patient was set 0.5 ng/mL higher than the previous patient.

Time to extubation was defined as the duration from the end of surgery and stop of inhalational agent to extubation. The MAC of end-tidal inhalational agent was recorded when the patients opened their eyes on verbal command. Respiratory complications including hypoventilation (respiratory rate <8 breaths/minute), laryngospasm, and desaturation (saturation <95%) for 3 minutes after extubation were recorded. Sedation score using the Ramsay Sedation Scale (six levels; 1=Anxious and agitated or restless or both, 6=No response to a light glabellar tap or loud auditory stimulus)<sup>24</sup> and nausea, vomiting, and pain score using numeric rating scale (NRS) (0=none, 10=the worst) were assessed at 30 minutes after PACU arrival. Fentanyl of 0.5 mcg/kg was administered when an NRS was 5 or greater.

## Statistical analysis

The primary outcomes were the effective concentration of remifentanyl to prevent emergence cough in 50% of patients

(EC<sub>50</sub>) and in 95% of patients (EC<sub>95</sub>). The EC<sub>50</sub> by the Dixon's up-and-down method needs at least six pairs of success-failure, and 20 patients were calculated as mean by midpoints of remifentanyl Ce of six success-failure pairs.<sup>25</sup> The EC<sub>50</sub> was compared between the two groups using independent *t*-test. The EC<sub>50</sub> and EC<sub>95</sub> were also calculated by isotonic regression method based on a pooled-adjacent-violators algorithm (PAVA) and 83% and 95% CIs were estimated through a bootstrapping approach.<sup>26</sup> If the EC<sub>50</sub> and EC<sub>95</sub> did not overlap at the 83% CIs and 95% CIs, the values were regarded as showing statistical differences.<sup>25,27</sup>

The secondary outcomes were time to extubation; respiratory complications during emergence including bradypnea, laryngospasm, and desaturation; sedation score; NRS; and the number of patients receiving fentanyl at the PACU. Of the secondary outcomes, categorical variables including respiratory complications during emergence; sedation score; and the number of patients receiving fentanyl at the PACU were presented as number and frequency. They were compared using chi-squared test or Fisher's exact test. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Continuous variables showing normality such as age, height, weight, and BMI were analyzed using Student's *t*-test and expressed as mean ± SD. Continuous variables not showing normality such as time to extubation, operation time, anesthetic time, sevoflurane volume percentile at eye opening, and NRS at the PACU were analyzed using the Mann–Whitney test and expressed as median (IQR). The repeated measures variables over time including HR and MAP were analyzed using a linear mixed model. Time and group were entered as interaction terms and the crossover effect was analyzed. A *P*-value of <0.05 was considered statistically significant. The SPSS package (version 23.0, IBM Corporation, Armonk, NY, USA) including R (version 3.2.5, The R foundation for Statistical Computing; <https://www.r-project.org>) was used for statistical analyses.

## Results

By Dixon's up-and-down method, the patients were randomly, sequentially allocated and enrolled until they reached six success-failure pairs. A total of 43 patients were assessed. One patient was missing data in PACU but was not withdrawn because we could assess preoperative and intraoperative data from the patient. Finally, 22 and 21 patients were enrolled in the sevoflurane and the desflurane groups without withdrawal, respectively. The CONSORT flow chart is shown in Figure 1. Demographics of patients and operation details

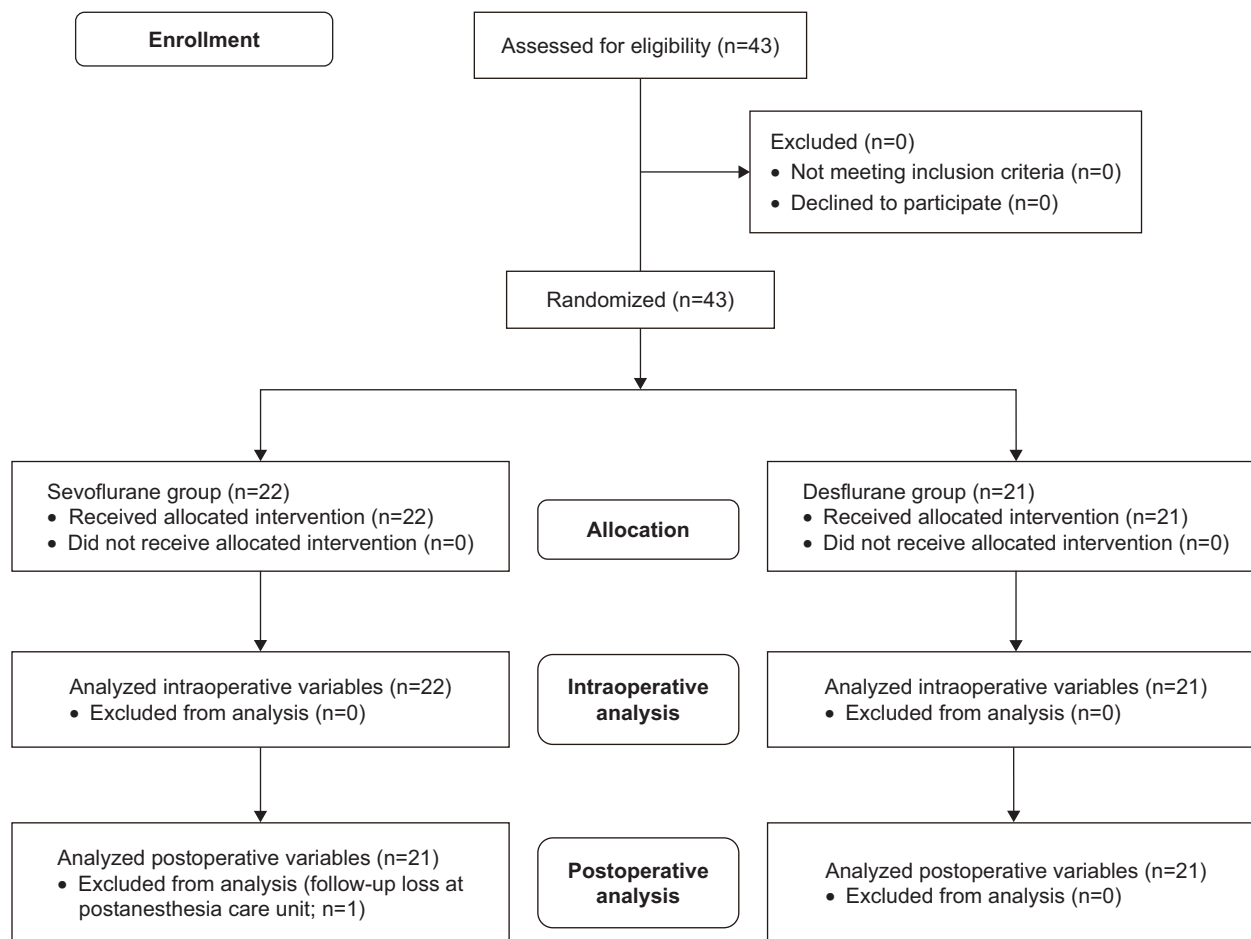


Figure 1 The CONSORT flow diagram.

were not significantly different between the two groups (Table 1).

The success and failure of smooth emergence are presented in Figure 2. Isotonic regression curve based on PAVA response rate is shown in Figure 3. The EC<sub>50</sub> by Dixon’s method and the EC<sub>50</sub> and EC<sub>95</sub> by isotonic regression are described in Table 2. The EC<sub>50</sub> of remifentanyl to prevent emergence cough by Dixon’s method was analyzed

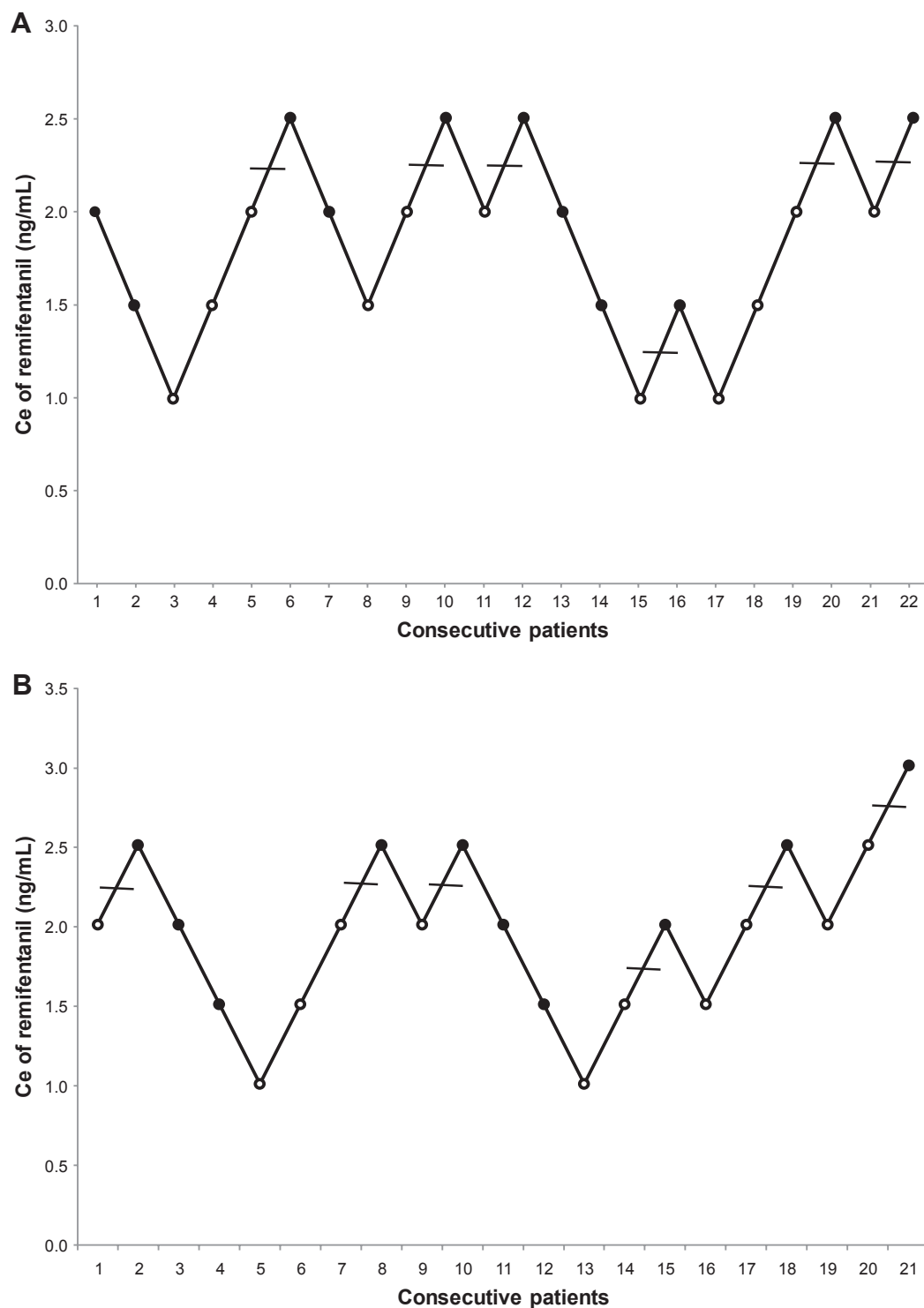
as mean from midpoints of pairs from failure to success and the two groups were comparable (2.08±0.47 ng/mL in the sevoflurane group and 2.25±0.40 ng/mL in the desflurane group, P=0.385). Using isotonic regression based on the PAVA response rate, the EC<sub>50</sub> (83% CIs) and EC<sub>95</sub> (95% CIs) values of remifentanyl to prevent emergence cough were 2.06 (1.45–2.23) ng/mL and 2.46 (2.35–2.48) in the sevoflurane group and 2.14 (1.45–2.56) ng/mL and 2.88 (2.47–2.98) in the desflurane group, respectively. They were also comparable between two groups because the 83% and 95% CIs were overlapped. The MAP and the HR at each time point are presented in Figure 4. The MAP did not show any significant difference according to time and group (P=0.649). However, the HR was significantly higher during emergence period in the desflurane group than in the sevoflurane group (P=0.019).

The emergence and recovery outcomes are presented in Table 3. The time to extubation and MAC when eyes are open were comparable between the two groups. Among respiratory complications, five patients in the

Table 1 Patients’ characteristics and intraoperative details

Variables	Sevoflurane (n=22)	Desflurane (n=21)
Age, years	66.5±4.4	67.1±5.1
Height, cm	156.8±5.0	153.9±5.4
Weight, kg	61.8±8.2	57.9±6.2
Body mass index, kg/m <sup>2</sup>	25.1±3.2	24.5±2.4
ASA classification I/2, n	6/16	9/12
Intubation attempts once/twice, n	19/3	18/3
Operation time, min	53 (39–60)	40 (25–65)
Anesthesia time, min	90 (65–100)	70 (58–95)

Note: Values are mean ± SD, median (IQR), or number. Abbreviation: ASA, American Society of Anesthesiologists.



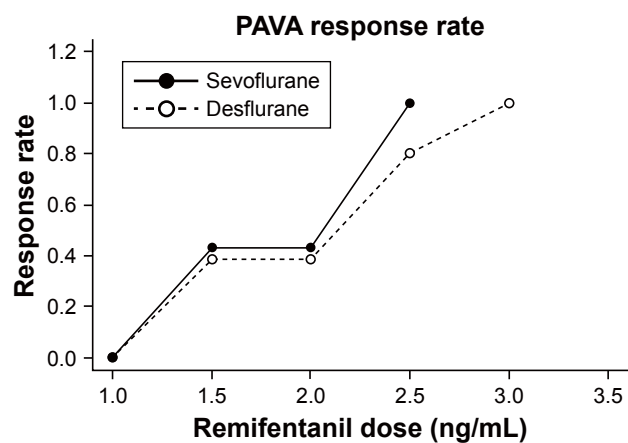
**Figure 2** Sequences of effect-site concentration (Ce) of remifentanyl to prevent emergence cough following extubation by Dixon's up-and-down method.

**Notes:** Horizontal lines represent crossover midpoints (ie, success to failure). The mean  $EC_{50}$  of remifentanyl Ce for suppressing emergence cough was calculated from crossover pairs of successes (closed circle) and failures (open circle) in (A) 22 patients of sevoflurane group and (B) 21 patients of desflurane group. The  $EC_{50}$  was  $2.08 \pm 0.47$  ng/mL in sevoflurane group and  $2.25 \pm 0.40$  ng/mL in desflurane group ( $P=0.385$ ).

sevoflurane group and two patients in the desflurane group showed bradypnea within 3 minutes after extubation. Those in the sevoflurane group consisted of one patient each at 1.0 ng/mL and 2.5 ng/mL of remifentanyl Ce,

two at 2.0 ng/mL, and one at 2.5 ng/mL. Those in the desflurane group all showed bradypnea at 2.0 ng/mL of remifentanyl Ce. However, all seven patients who showed bradypnea responded to encouragement of breathing and no-one showed





**Figure 3** Pooled-adjacent-violators algorithm (PAVA) response rates in sevoflurane group (closed circle) and desflurane (open circle) patients.

**Note:** The PAVA response rate mean ratio of the number of successful patients to the number of total patients at each remifentanyl Ce in each group.

laryngospasm or desaturation. At the PACU, respiratory complications did not occur, and sedation status was observed within the range of awake levels (sedation scores 1, 2, and 3).

## Discussion

In this study, we investigated the Ce of remifentanyl for preventing cough during emergence from general anesthesia in elderly female patients, according to inhalational agents (sevoflurane or desflurane). We found that  $EC_{50}$  and  $EC_{95}$  for preventing cough during emergence by the Dixon's method or isotonic regression method did not show significant differences between sevoflurane and desflurane anesthesia in elderly female patients.

Cough reflex and the effect of opioid were known to differ according to sex.<sup>15,16,28</sup> Several studies demonstrated that the remifentanyl Ce preventing emergence cough showed significant differences according to sex.<sup>19-21</sup> Along with sex, aging also was known to be related to cough reflex.<sup>15,16</sup>

**Table 2** Ce of remifentanyl for suppressing emergence cough following extubation

Variables	Sevoflurane group (n=22)	Desflurane group (n=21)
Dixon's method		
$EC_{50}$ of remifentanyl Ce (ng/mL)	2.08±0.47	2.25±0.40
Isotonic regression method		
$EC_{50}$ of remifentanyl Ce (ng/mL)	2.06 (1.45–2.23)	2.14 (1.45–2.56)
$EC_{95}$ of remifentanyl Ce (ng/mL)	2.46 (2.35–2.48)	2.88 (2.47–2.98)

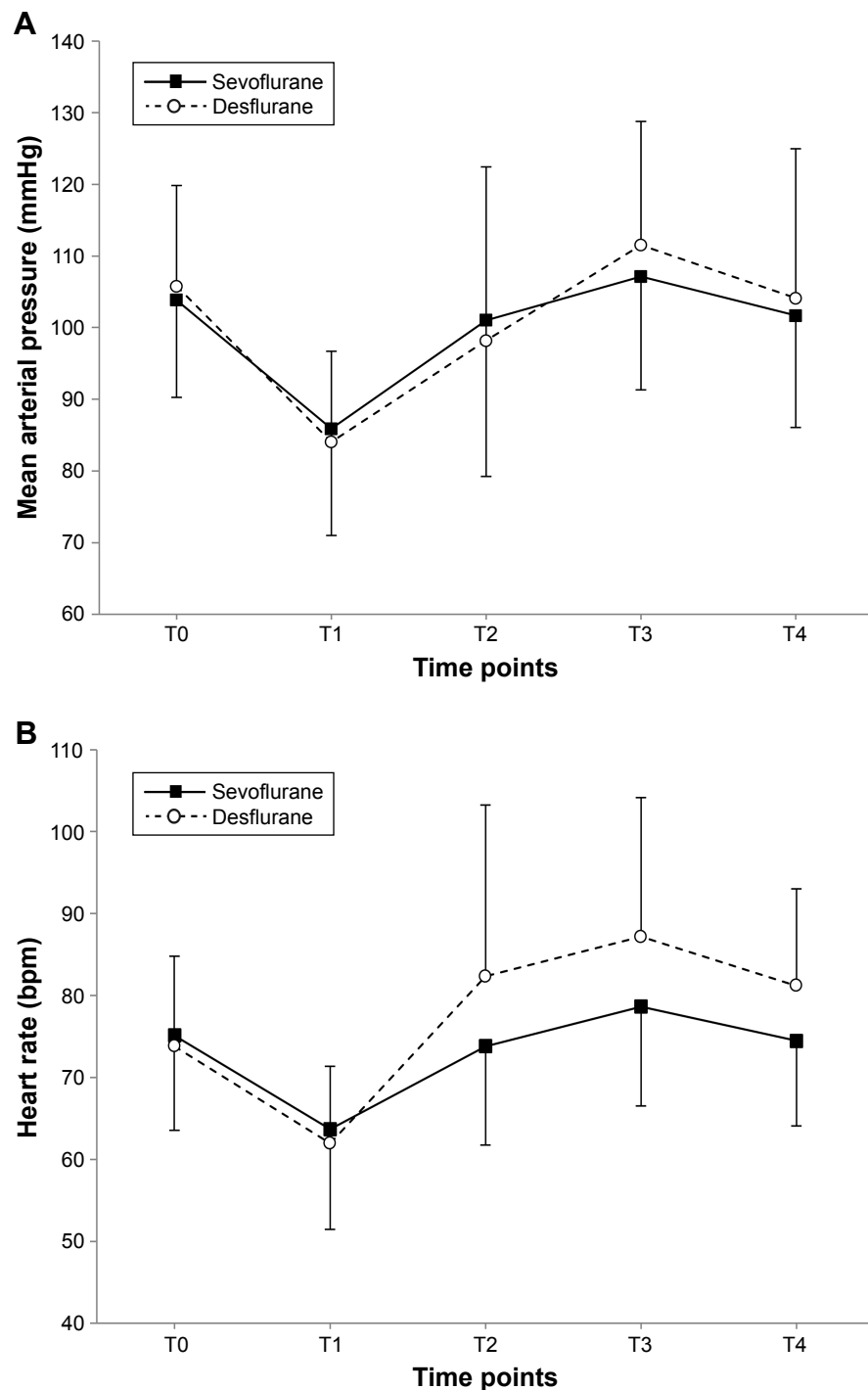
**Note:** Values are mean ± SD determined by Dixon's method and the  $EC_{50}$  (83% CI) and  $EC_{95}$  (95% CI) determined by the isotonic regression method.

**Abbreviation:** Ce, effect-site concentration.

and the effect of opioid.<sup>29,30</sup> Recently, Yoo et al reported no difference in the remifentanyl Ce between adult and elderly patients during emergence from sevoflurane anesthesia.<sup>12</sup> However, the influence of aging on remifentanyl Ce could not be confirmed because Yoo et al included both male and female patients. The elderly patients are more vulnerable to adverse effects of opioid than young adult patients.<sup>31</sup> Finally, emergence cough is especially more dangerous in elderly patients due to multiple comorbidity. Therefore, we included only elderly female patients as subjects in this study, considering the influences of age and sex on evaluating remifentanyl Ce to prevent emergence cough.

It is widely believed that desflurane provokes upper airway irritation including coughing and laryngospasm.<sup>32</sup> A meta-analysis revealed that desflurane caused a higher incidence of emergence cough than sevoflurane.<sup>33</sup> In this study, the  $EC_{50}$  of remifentanyl by Dixon's method and the  $EC_{50}$  and  $EC_{95}$  by isotonic regression method to prevent emergence cough were comparable between sevoflurane group and desflurane group among elderly female patients. These results are consistent with those of Lee et al's study that evaluated the remifentanyl Ce to prevent emergence cough according to anesthetic agents in young and middle aged (20–65 years) female patients.<sup>22</sup> Therefore, it may be suggested that the remifentanyl Ce preventing emergence cough is similar regardless of the type of inhalational agents in female patients.

With regard to our comparable remifentanyl Ce between sevoflurane and desflurane, there are some possible explanations. First, because endotracheal tube is regarded as a relatively more potent airway irritant compared with inhalational agents, the degree of pungency between sevoflurane and desflurane would have been negligible. Actually, most of the studies, which reported significant difference of emergence cough between two inhalational agents, were performed on patients using facial mask or laryngeal mask airway and not on endotracheal intubation.<sup>17,34,35</sup> However, the evaluation of the remifentanyl Ce between sevoflurane and desflurane is of great clinical importance because the intubated patients generally have greater medical complexity compared with those managed with laryngeal mask airway and thus are exposed to a greater risk of adverse events regarding extubation. Second, the simultaneous administration of opioid might decrease airway response regardless of the type of inhalational agents. The aforementioned studies, which reported significant differences in emergence cough according to inhalational agents, did not use opioid with inhalational agents around the end of surgery and emergence.<sup>17,34,35</sup> Whereas other studies, which did



**Figure 4** The (A) MAP and (B) HR during perioperative period.

**Notes:** Data are expressed as mean  $\pm$  SD. The MAP did not show any significant difference between the two groups according to time and group ( $P=0.649$ ). However, the HR was significantly higher during emergence period in the desflurane group than in the sevoflurane group ( $P=0.019$ ).

**Abbreviations:** HR, heart rate; MAP, mean arterial pressure; T0, before induction; T1, end of operation; T2, just before extubation; T3, just after extubation; T4, 3 minutes after extubation.

not show significant differences between two inhalational agents, used inhalational agents with opioids such as fentanyl or remifentanyl.<sup>14,22,36</sup> Therefore, the remifentanyl infusion during emergence would decrease the distinction of influences according to inhalational agents. Third, in this

study, sugammadex was administered for reversal of muscle relaxant in all patients. Cough is one of the commonly reported adverse events with sugammadex.<sup>37</sup> It should be distinguished from previous studies using neostigmine or pyridostigmine to reverse muscle relaxation.

**Table 3** Emergence and recovery outcomes

Variables	Sevoflurane	Desflurane	P-value
During emergence	N=22	N=21	
Time to extubation, min	510 (300–805)	424 (369–685)	0.413
Concentration of volatile agent at eye opening, %	0.2 (0–0.3)	0.4 (0.3–0.7)	<0.001
MAC of volatile agent at eye opening	0.1 (0–0.2)	0.1 (0.1–0.1)	0.582
Respiratory complications, n (%)			0.412
Bradypnea	5 (23)	2 (10)	
Laryngospasm	0	0	
Desaturation	0	0	
At postanesthesia care unit	N=21	N=21	
Sedation score 1/2/3, n	2/16/3	0/20/1	0.216
PONV	2 (10)	1 (5)	>0.999
Pain score using NRS	4 (3–7)	5 (3–6)	0.729
Patients receiving fentanyl	9 (43)	12 (57)	0.355

**Notes:** Values are mean  $\pm$  SD, median (IQR), or number (%). Sedation score was recorded by Ramsay Sedation Scale with a range from 1 to 6.

**Abbreviations:** MAC, minimal alveolar concentration; PONV, postoperative nausea and vomiting; NRS, numeric rating scale.

Meanwhile, we had performed similar designed study to evaluate sex-related differences in remifentanyl Ce for preventing emergence cough in elderly patients.<sup>19</sup> Comparing the EC<sub>50</sub>s in elderly female patients between this study and previous study, the EC<sub>50</sub>s seem to be quite different despite similar study circumstances (2.14 vs 1.67 ng/mL). However, the comparison of absolute values may be inappropriate because of the differences between the practitioners or the differences between pairs chosen for EC<sub>50</sub> (eg, success-failure pairs or failure-success pairs).

Although desflurane was known to have a more rapid awakening and a faster recovery of airway reflex,<sup>32</sup> time to extubation and MAC of inhalational agents at eye opening did not show significant difference between two groups in this study. On the contrary, although a balanced anesthesia with desflurane and remifentanyl had been shown to conceal a desflurane-induced increase in HR,<sup>38</sup> this study showed significant increases in HR in desflurane group compared with sevoflurane group during emergence period (Figure 4). However, this study targeted the remifentanyl Ce by Dixon's method as primary outcomes; the results of secondary outcomes were not specifically powered. To evaluate secondary outcomes, a large volume study is needed that targeted these values.

There were several limitations in this study. First, this study was not double-blinded design. Because the outcome assessors in the operating room were not blinded to predetermined remifentanyl Ce, it is possible to affect in-room outcomes. Second, the EC<sub>50</sub> of remifentanyl by isotonic regression method was calculated from 22 patients' and 21 patients' groups by Dixon's up-and-down allocation method. Because CIs by isotonic regression are more precise at a large sample size, the difference at the EC<sub>50</sub> of remifentanyl by isotonic

regression method may not be reliable.<sup>25</sup> Third, because the elderly patients have a large individual variation of biologic capacity, the concealed comorbidities may affect the results. Fourth, although the sugammadex was administered in two groups equally, it was difficult to completely exclude the effect of sugammadex on cough.

## Conclusion

Despite the airway irritant property of desflurane, there was no difference in the remifentanyl Ce to prevent emergence cough between sevoflurane and desflurane anesthesia. Therefore, the clinicians may not need to adjust the remifentanyl Ce to prevent emergence cough according to inhalational agents in elderly female patients.

## Disclosure

The authors report no conflicts of interest in this work.

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